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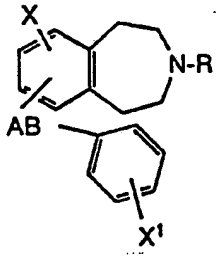


(I)

(57) Abstract

Alpha-adrenergic receptor antagonists having formula (I), which are useful to produce α-adrenoceptor antagonism, pharmaceutical compositions including these antagonists, and methods of using these antagonists to produce α-adrenoceptor antagonism in mammals.

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# CHEMICAL COMPOUNDS

## FIELD OF THE INVENTION

This invention relates to novel substituted 2,3,4,5-tetrahydro-1H-3-benzazepine compounds having α-adrenergic receptor antagonist activity.

## BACKGROUND OF THE INVENTION

The autonomic nervous system is separated into the cholinergic and adrenergic nervous systems. Norepinephrine, the neurotransmitter of the adrenergic nervous system, exerts its activity by interaction with receptors (adrenoceptors) on the effector organs or on the nerve endings. The adrenoceptors are of two primary types: α and ß. Based upon selectivity of the receptors for a series of agonists and antagonists, the a adrenoceptors have been subdivided into $\alpha_1$ and $\alpha_2$ subtypes.

A large amount of experimental evidence now supports the view that the $\alpha_2$ subtype is a heterogeneous adrenoceptor class. (For a general review see Timmermans and Van Zwieten, J. Med. Chem., 25, 1389 (1982)). Experiments using 6-chloro-9-(3-methyl-2-butenyloxy)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (SK&F 104078) demonstrated that the classical adrenoceptors are heterogeneous and can be divided into SK&F 104078-

insensitive and SK&F 104078-sensitive $\alpha_2$ adrenoceptors. The latter variously are referred to as postjunctional $\alpha_2$ adrenoceptors or, preferably, $\alpha_3$ adrenoceptors, United States Patent No. 4,683,229, July 28, 1987.

As one of the primary regulators of peripheral vascular tone, $\alpha$ adrenoceptors long have been the targets of efforts to develop agents effective in changing vascular tone for use in treating diseases, such as hypertension, in which alterations in vascular resistance produce therapeutic benefits. Antihypertensive compounds presently in clinical use that function via interaction with a adrenoceptors include methyldopa, clonidine, and prazosin. Efforts to modulate sympathetic tone through interactions with a adrenoceptors have resulted in several compounds that interact somewhat selectively with $\alpha_1$ or $\alpha_2$ adrenoreceptors. Selective agonists include phenylephrine and methoxamine which preferentially activate $\alpha_1$ receptors; and clonidine, $\alpha$-methyl-norepinephrine, and tramazoline which preferentially activate $\alpha_2$ adrenoceptors. Examples of selective $\alpha$-adrenoceptor antagonists include prazosin which has high selectivity for $\alpha_1$ adrenoceptors; and the $\alpha_2$-selective blockers yohimbine and rauwolscine.

United States Patent No. 4,469,634, dated September 4, 1984, describes allyloxy- and allythio- 2,3,4,5-tetrahydro-1H-3-benzazepines useful as intermediates for preparing $\alpha_2$ adrenoceptor affinity resins and as antihypertensive agents.

U.S. Patent No. 4,683,229 dated July 28, 1987, describes 6-halo-9-alkenyloxy-2,3,4,5-tetrahydro-1H-3-benzazepines having $\alpha_3$-selective antagonist activity.

U.S. Patent No. 4,265,890 dated May 5, 1981, describes mercapto substituted-2,3,4,5-tetrahydro-1H-3-benzazepines having dopamine receptor blocking activity.

Kaiser, et al., in J. Med. Chem., 23:975-976 (1980) describes the preparation of 6-(phenylthio)-substituted-

2,3,4,5-tetrahydro-1H-3-benzazepines that are dopamine receptor antagonists.

Ku, et al., in J. Org. Chem. 47:3862-3865 (1982) details the synthesis of certain arylthio-substituted-2,3,4,5-tetrahydro-1H-3-benzazepines. These compounds are neuroleptic agents functioning as dopamine receptor antagonists.

## SUMMARY OF THE INVENTION

The present invention resides in the discovery that certain substituted-2,3,4,5,-tetrahydro-1H-3-benzazepine compounds are α-adrenoceptor antagonists. Presently preferred compounds of the invention include:

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-phenoxy-1H-3-benzazepine,

6-chloro-2,3,4,5-tetrahydro-9-[(4-methoxyphenyl)-methoxy]-3-methyl-1H-3-benzazepine,

6-chloro-9-[(2,6-dimethoxyphenyl)methoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine,

6-chloro-9-[(4-chlorophenyl)methoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine,

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-(2-phenylethoxy)-1H-3-benzazepine,

6-chloro-2,3,4,5-tetrahydro-9-[2-(2-methoxyphenyl)ethoxy]-3-methyl-1H-3-benzazepine,

6-chloro-2,3,4,5-tetrahydro-9-[2-(3-methoxyphenyl)ethoxy]-3-methyl-1H-3-benzazepine,

6-chloro-2,3,4,5-tetrahydro-9-[2-(3,4-dimethoxyphenyl)ethoxy]-3-methyl-1H-3-benzazepine,

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[(3-phenyl-2-propenyl)oxy]-1H-3-benzazepine,

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[2-phenoxyethoxy]-1H-3-benzazepine,

6-chloro-9-[2-(2,6-dimethoxyphenoxy)ethoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine,

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[4-(4-nitrophenyl)butoxy]-1H-3-benzazepine,

9-[4-(4-aminophenyl)butoxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine,

9-[4-(4-amino-3-iodophenyl)butoxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine,

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[((3-(4-nitrophenyl)propyl)carbonyl)oxy]-1H-3-benzazepine,

9-[((3-(4-aminophenyl)propyl)carbonyl)oxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine, and

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-(3-phenylpropyl)-1H-3-benzazepine; or a pharmaceutically acceptable salt thereof.

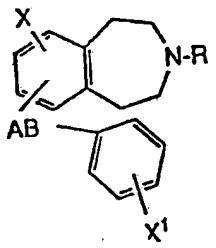
The most preferred compound of the invention is 6-chloro-2,3,4,5-tetrahydro-3-methyl-9-(2-phenylethoxy)-1H-3-benzazepine or a pharmaceutically acceptable salt thereof.

In a further aspect of the invention there are provided methods of antagonizing a adrenoceptors in mammals, including humans, that comprise administering internally to a subject an effective amount of a substituted 2,3,4,5-tetrahydro-1H-3-benzazepine compound.

Included in the present invention are pharmaceutical compositions comprising compounds useful in the method of the invention and a suitable pharmaceutical carrier. Preferably, these compositions are used to produce a adrenoceptor antagonism and contain an effective amount of compounds useful in the methods of the invention.

## DETAILED DESCRIPTION OF THE INVENTION

The presently invented compounds that are α-adrenoceptor antagonists or are useful in preparing α-adrenoceptor antagonists are represented by the following Formula (I):




(I)

in which:

X is H, Cl, Br, F, I, $CF_3$, $C_{1-6}$alkyl, $COR^1$, $CO_2R^2$, $CONR^2R^2$, CN, $NO_2$, $NR^3R^4$, $OR^3$, $SR^1$, $SCF_3$, or any accessible combination thereof up to three substituents;

R is H, $C_{1-6}$alkyl, or $C_{3-5}$alkenyl;

B is absent or present as O or S;

A is $-OCO(CH_2)_{1-4}-$, $-OCH_2CH=CH-$, $-CO_2(CH_2)_{1-4}-$, $-(CH_2)_{0-6}-$, or $-(CH_2)_nZ(CH_2)_m-$, wherein when B is absent, n is 0-4 and m is 0-5, with the proviso that m and n taken together are no greater than 5, and when B is present, n is 0-4 and m is 1-5, with the proviso that m and n taken together are no greater than 5;

Z is O or S;

each $R^1$ independently is $C_{1-6}$alkyl or $(CH_2)_{0-6}$phenyl;

each $R^2$ independently is H, $C_{1-6}$alkyl, or $(CH_2)_{0-6}$phenyl;

$R^3$ is H, $C_{1-6}$alkyl, CHO, $COR^1$, or $SO_2R^1$;

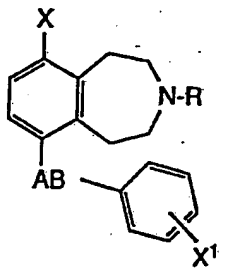
$R^4$ is H or $C_{1-6}$alkyl; and

$X^1$ is H, Cl, Br, F, I, $CF_3$, $C_{1-6}$alkyl, $COR^1$, $CO_2R^2$, $CONR^2R^2$, CN, $NO_2$, $NR^3R^4$, $OR^3$, $SR^1$, $SCF_3$ or any accessible combination thereof up to five substituents;

or a pharmaceutically acceptable salt thereof, provided that when X is H taken three times, Cl, Br, F, $CF_3$, $CH_3$, $OCH_3$, di-$OCH_3$, OH, di-OH, $NO_2$, $NH_2$, $OC(O)C_{1-6}$alkyl, or di-$CO(O)C_{1-6}$alkyl, B is absent, and A is S, $X^1$ is not H taken five times, Cl, di-Cl, F, OH, $NO_2$, $CH_3$, $CF_3$, or $OCH_3$.

As used herein $C_{1-6}$alkyl means straight or branched alkyl of one to six carbon atoms, $C_{3-5}$alkenyl means a straight or branched chain alkenyl having from 3 to 5 carbon atoms, and "any accessible combination thereof" means any combination of up to three substituents on the phenyl moiety that is available by chemical synthesis and is stable.

Formula (Ia) includes presently preferred Formula (I) compounds:




(Ia)

in which:

X is H, Cl, Br, F, I, $CF_3$, $C_{1-6}$alkyl, $COR^1$, $CO_2R^2$, $CONR^2R^2$, CN, $NO_2$, $NR^3R^4$, $OR^3$, $SR^1$, or $SCF_3$,

R is H, $C_{1-6}$alkyl, or $C_{3-5}$alkenyl;

B is absent or present as O or S;

A is $-OCO(CH_2)_{1-4}-$, $-OCH_2CH=CH-$, $-CO_2(CH_2)_{1-4}-$, $-(CH_2)_{0-6}-$, or $-(CH_2)_nZ(CH_2)_m-$, wherein when B is absent, n is 0-4 and m is 0-5, with the proviso that m and n taken together are no greater than 5, and when B is present, n is 0-4 and m is 1-5, with the proviso that m and n taken together are no greater than 5;

Z is O or S;

each $R^1$ independently is $C_{1-6}$alkyl or $(CH_2)_{0-6}$phenyl;

each $R^2$ independently is H, $C_{1-6}$alkyl, or $(CH_2)_{0-6}$phenyl;

$R^3$ is H, $C_{1-6}$alkyl, CHO, $COR^1$, or $SO_2R^1$;

$R^4$ is H or $C_{1-6}$alkyl; and

$X^1$ is H, Cl, Br, F, I, $CF_3$, $C_{1-6}$alkyl, $COR^1$, $CO_2R^2$, $CONR^2R^2$, CN, $NO_2$, $NR^3R^4$, $OR^3$, $SR^1$, $SF_3$, or any accessible combination thereof up to five substituents;

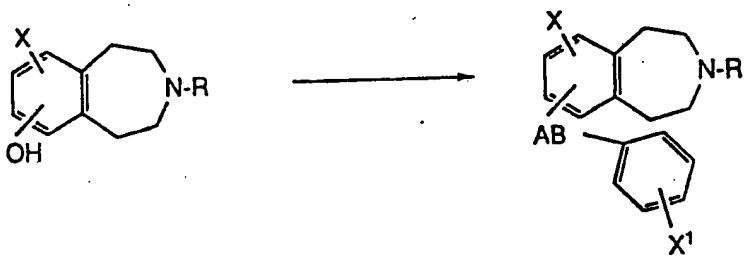
or a pharmaceutically acceptable salt thereof, provided that when X is H, Cl, Br, F, $CF_3$, $CH_3$, $OCH_3$, OH, $NO_2$, $NH_2$, or $OC(O)C_{1-6}$alkyl, B is absent, and A is S, $X^1$ is not H taken five times, Cl, di-Cl, F, OH, $NO_2$, $CH_3$, $CF_3$, or $OCH_3$.

Preferred compounds are represented by Formula (Ia) when:

X is Cl, Br, F, or I; and

R is $CH_3$.

Scheme I




(1) (I)

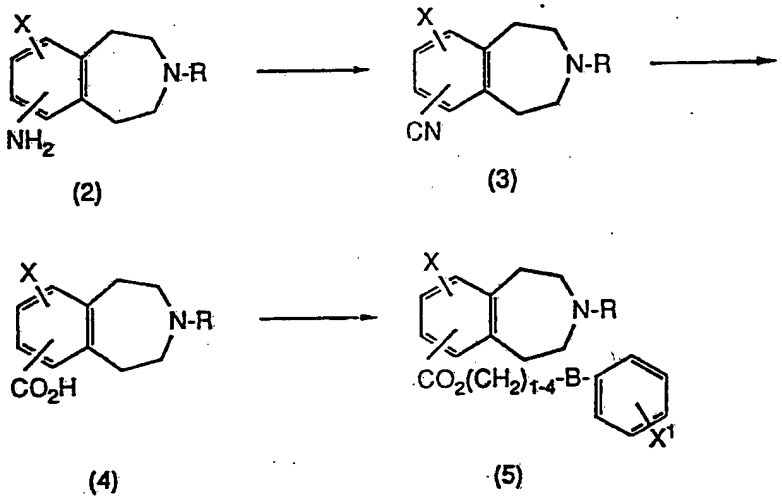
The benzazepines of formula (1) are described in published references, such as J. Med. Chem., 27:918-921 (1984), or can be obtained readily using known procedures. According to Scheme I, the starting compounds of formula (1) are added to a suitable base, such as an alkali metal hydride, for example, sodium hydride, in a suitable organic solvent, such as dimethylformamide. Thereafter, an appropriately substituted halide or sulfonate, such as 2-phenylethyl bromide, cinnamyl chloride, 2-(phenoxy)ethylbromide, or 2-(2-methoxyphenyl)ethyl-4-methylbenzenesulfonate, is reacted with the above-generated intermediate to produce Formula (I) compounds wherein A is $-O(CH_2)_{1-5}-$ or $-OCH_2CH=CH-$ and B is absent or present as O or S.

Formula (I) compounds wherein B is absent and A is -O- are prepared by reacting formula (I) compounds with a $X^1$-substituted diphenyliodonium halide, such as diphenyliodonium chloride, in the presence of copper and a suitable base, such as triethylamine, in a suitalbe solvent, such as methanol.

Formula (I) compounds wherein A is $-OCO(CH_2)_{1-4}-$ are prepared also from formula (I) compounds. In this process, the starting alcohol compounds are reacted with a ($X^1$-substituted-phenyl)alkanoyl halide, such as 4-(4-nitrobenzene)butanoyl chloride, in the presence of a

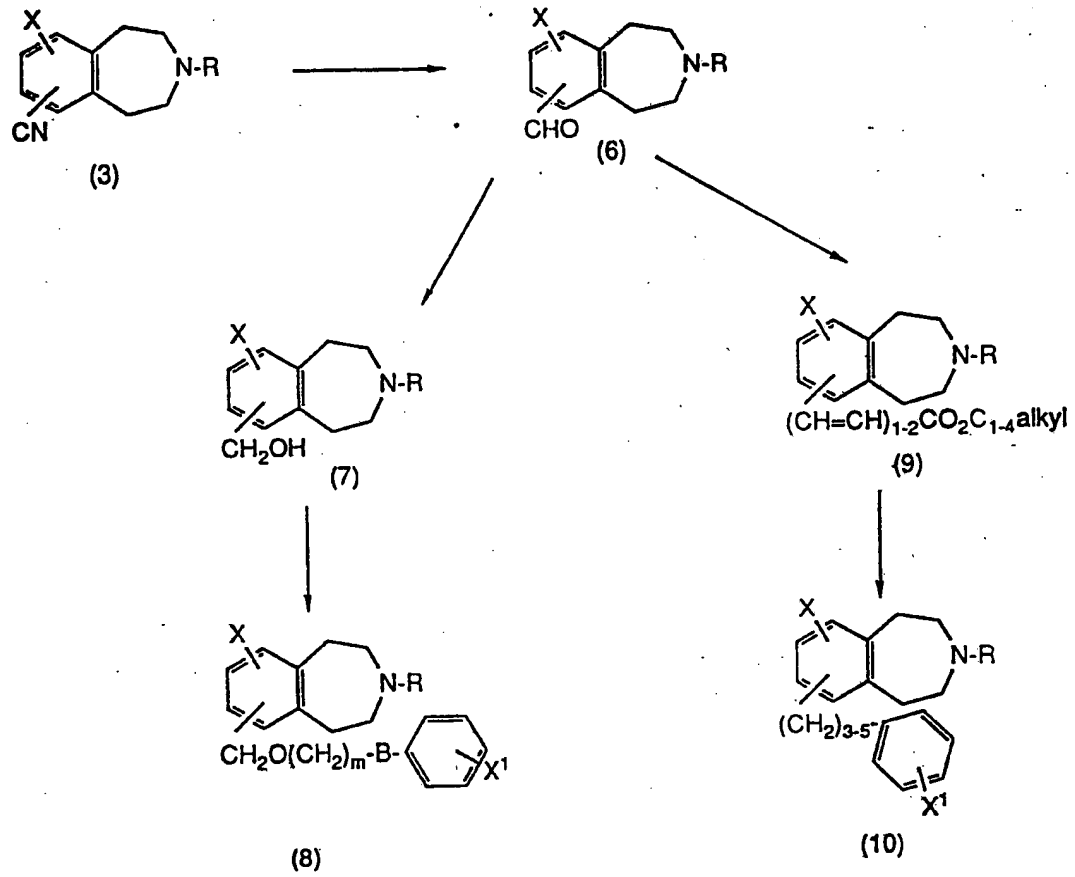
base, such as triethylamine, in a suitable solvent, such as methylene chloride.

Scheme II




The benzazepines of formula (2) are known to the art (J. Med. Chem., 27:918-921 (1984)) or are synthesized by known procedures. According to Scheme II, the primary amine of formula (2) compounds is diazotized using, for example, sodium nitrite in acetic acid, water, and sulfuric acid. Conversion to the corresponding cyano compounds of formula (3) is accomplished by reacting the diazonium salt with cyanide, for example, potassium cyanide. The carboxylic acid compounds of formula (4) are prepared by reacting the cyano of the formula (3) compounds in the presence of barium hydroxide, in a suitable solvent, such as a mixture of ethanol and water. The resulting acids are reacted with a suitable base, such as an alkali metal hydride, such as sodium hydride, in an appropriate solvent, such as dimethylformamide. Thereafter, reaction with an appropriately substituted halide, such as 4-chloro-1-chloromethylbenzene, gives formula (5) compounds, which are Formula (I) compounds wherein A is $-CO_2(CH_2)_{1-4}-$.

Scheme III




Scheme III illustrates the preparation of additional Formula (I) compounds. According to Scheme III, formula (3) cyano compounds are converted to the corresponding aldehyde derivatives of formula (6), for example using Raney® nickel in a suitable solvent, such as formic acid, at a temperature of about 35°C to about 100°C, preferably at about 100°C. The formula (7) hydroxymethyl benzazepines are prepared from the formula (6) aldehyde compounds by reductive methods, for example, using sodium borohydride in a suitable solvent, such as methanol, at a temperature from about 0°C to about 35°C, preferably from about 5°C to about 24°C. Formula (8) benzazepines, which

are Formula (I) compounds, are prepared from formula (7) benzazepines, using the methods described in Scheme I.

Scheme III also shows the preparation of Formula (I) compounds wherein A is $-(CH_2)_{3-5}-$ and B is absent. According to Scheme III, formula (6) aldehyde compounds are reacted with a phosphorus ylide, such as triphenylphosphoranylideneacetaldehyde, in a suitable solvent, such as toluene, at a temperature of about 80°C to about 110°C, preferably at 110°C, or with an alkylphosphonic ester, such as triethyl phosphonoacetate, which is converted to a phosphonate carbanion in reaction with a suitable base, such as sodium hydride, in a suitable solvent, such as tetrahydrofuran, to give the corresponding alkenyl derivatives, for example -CH=CH-CH=CH-CHO or $-CH=CHCO_2$ethyl, respectively. The vinyl intermediates thus generated are reduced to the corresponding saturated analogs, for example by hydrogenation in the presence of a suitable catalyst, such as platinum oxide, in a suitable solvent, such as ethanol. The terminal ester or formyl groups are reduced to the corresponding alcohol derivatives using standard reagents, for example, an ester-reducing agent, such as lithium aluminum hydride, or a formyl-reducing agent, such as sodium borohydride. The alcohols are reacted with a halogenating agent, such as thionyl chloride, to give $-(CH_2)_{3-5}$halo benzazepines. Reaction of the halo benzazepines with a $X^1$-substituted phenyllithium compound, in the presence of cuprous bromine, gives Formula (I) compounds wherein A is $-(CH_2)_{3-5}-$ and B is absent.

The pharmaceutically acceptable, nontoxic, acid addition salts having the utility of the free bases of Formula (I), are formed with inorganic or organic acids, by methods well known in the art. Representative examples of suitable acids are maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic,

hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

Because the compounds of Formula (I) are α-adrenoceptor antagonists they are useful in treating cardiovascular diseases in which changes in vascular resistance are desirable, including hypertension, pulmonary hypertension, congestive heart failure, peripheral vascular disease, myocardial ischemia, and angina pectoris. Formula (I) compounds also are useful in treating benign prostatic hypertrophy, diabetes, glaucoma, ocular hypertension, obesity, disorders of gastrointestinal motility, including colonic spasm, irritable bowel syndrome, and constipation, impotence, and central nervous system disorders such as depression and senile dementia. Additionally, the invented compounds are useful in treating diseases resulting from inappropriate platelet aggregation.

The α-adrenoceptor activity of certain compounds of the present invention was determined using the following in vitro systems.

Alpha$_1$ adrenoceptor antagonist activity was determined using the rabbit aorta. Male New Zealand White rabbits (2-4 Kg) were euthanized by cervical concussion. A 4 cm portion of the thoracic aorta was removed and placed in a dish of cold (10°C) Krebs-Hensleit solution. The tissue was cleaned of fat and connective tissue and cut into segments of approximately 3 mm in length. These segments were suspended in 10 ml tissue baths via hangers constructed of 0.25 mm tungsten wire. One hanger was fixed to a support in the bath and the other was attached via silk thread to a force-displacement transducer.

Tissue segments were equilibrated for 2 hours prior to drug testing, during which time basal tension was maintained at 2 gm. Tissues were washed at 30 minute intervals during this equilibration period. The Krebs-Hensleit solution contained cocaine (6mM) to block neuronal uptake and propranolol (1mM) to block beta-

adrenoceptors. Tissues were usually challenged once with norepinephrine (0.1mM) during the equilibration period to check for viability.

A cumulative concentration-response curve to norepinephrine was obtained in each aortic segment. Following washout of norepinephrine, the a adrenoceptor antagonist to be tested was added to the bath. After the tissue had been in contact with the antagonist for 30-60 minutes, the norepinephrine concentration response-curve was repeated in the presence of antagonist. The tissue was then washed again, and a tenfold higher concentration of antagonist added. Following equilibration (30-60 minutes), a third norepinephrine concentration-response curve was determined in the presence of the antagonist.

The receptor dissociation constant ($K_\beta$) for the antagonist was determined using the relationship

$$K_\beta = \frac{\text{Antagonist Concentration}}{\text{Dose Ratio} - 1}$$

(Furchgott, R. F., Handbook of Experimental Pharmacology, eds. Eichler, et al., pp. 283-335 (Springer 1972)). The $K_\beta$ value obtained at each antagonist concentration was averaged to obtain a mean $K_\beta$ for each experiment.

Alpha$_2$ adrenoceptor antagonist activity of the compounds was determined using the isolated, superfused guinea pig left atrium. Briefly, the heart is removed from a pentobarbital-anesthetized male guinea pig. The left atrium is separated, dissected free of extraneous tissue and mounted in a 2 ml superfusion chamber. The tissue is paced at 30 pulse/minute and the sympathetic nerves excited at 6 minute intervals by field stimulation. The response to nerve stimulation is measured as the difference in contractile force between the basal contraction and peak contraction following a nerve stimulation. A concentration-response curve for B-HT 920 (a known $\alpha_2$ agonist) is prepared by administering

increasing concentrations of B-HT 920 following each successive stimulation. The tissue then is superfused for thirty minutes with the α-adrenoceptor antagonist to be tested and the B-HT 920 concentration-effect curve is repeated in the presence of antagonist. Data are reported as $K_B$, defined above. Additional details of this test system are found in Hieble, J. P. and R. G. Pendleton, Arch. Pharmacol., 309:217-224 (1979).

Alpha$_3$ adrenoceptor antagonist receptor activity was determined using the dog saphenous vein (DSV) as the test system. This test system has been shown a suitable preparation in which to characterize postsynaptic $\alpha_2(\alpha_3)$ adrenoceptors, Sullivan, A. T. and G. M. Drew, Arch. Pharmacol., 314:249-58 (1980). This test system is prepared by removing the lateral saphenous vein from an anesthetized dog and cutting the vein into segments of 4 mm in length. Segments are mounted as described for the isolated rabbit aorta.

The $\alpha_3$ adrenoceptor antagonist activity of the compounds of interest is determined by measuring shifts in the dose-response curve of a specific agonist induced by the tested compounds. The $\alpha_2$, $\alpha_3$ agonist, B-HT 920, was used in testing the compounds listed in Table I.

Representative Formula (I) compounds which were tested using the above described in vitro test systems are listed in Table I. Each of the compounds tested was found to have antagonist activity at one or more of the α-adrenoceptor subtypes.

Table I

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-phenoxy-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-9-[(4-methoxyphenyl)-methoxy]-3-methyl-1H-3-benzazepine;

6-chloro-9-[(2,6-dimethoxyphenyl)methoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

6-chloro-9-[(4-chlorophenyl)methoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-(2-phenylethoxy)-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-9-[2-(2-methoxyphenyl)ethoxy]-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-9-[2-(3-methoxyphenyl)ethoxy]-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-9-[2-(3,4-dimethoxyphenyl)ethoxy]-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[(3-phenyl-2-propenyl)oxy]-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[2-phenoxyethoxy]-1H-3-benzazepine;

6-chloro-9-[2-(2,6-dimethoxyphenoxy)ethoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[4-(4-nitrophenyl)butoxy]-1H-3-benzazepine;

9-[4-(4-aminophenyl)butoxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

9-[4-(4-amino-3-iodophenyl)butoxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[((3-(4-nitrophenyl)propyl)carbonyl)oxy]-1H-3-benzazepine;

9-[((3-(4-aminophenyl)propyl)carbonyl)oxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine; and

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-(3-phenylpropyl)-1H-3-benzazepine; or a pharmaceutically acceptable salt thereof.

The antihypertensive activity of certain compounds of the present invention was determined using the spontaneously hypertensive rat model. The details of this in vivo test are found in Roesler, J. M., et al., J. Pharmacol. Exp. Ther., 236:1-7 (1986).

Novel pharmaceutical compositions are obtained when the compounds are incorporated with pharmaceutical carriers into convenient dosage forms such as capsules,

tablets, or injectable preparations. Solid or liquid pharmaceutical carriers can be employed. Solid carriers include, starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid, or an aqueous or nonaqueous liquid suspension or solution.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating and compressing, when necessary, for tablet forms; or mixing, filling, and dissolving the ingredients, as appropriate, to give the desired oral or parenteral products.

Doses of the present compounds in pharmaceutical dosage units will be an efficacious, nontoxic quantity selected from the range of 0.01-100 mg/kg of active compound, preferably 0.1-50 mg/kg. The selected dose is administered to a human patient in need of treatment from 1-6 times daily, orally, rectally, topically, by inhalation, or injection, or continuously by infusion. Oral administration, however, is preferred because it is more convenient for the patient.

The following examples are illustrative of preparation of Formula (I) compounds. The examples are not intended to limit the scope of the invention as defined hereinabove and as claimed below.

Example 1

6-Chloro-2,3,4,5-tetrahydro-3-methyl-9-phenoxy-1H-3-benzazepine

A mixture of 9-chloro-2,3,4,5-tetrahydro-1H-3-benzazepin-6-ol (633 mg, 3 mmol), diphenyliodonium chloride (1.7 g, 5.4 mmol), triethylamine (1.3 ml) and copper powder (200 mg) in methanol (20 ml) was stirred at 40°C for 18 hours. The mixture was filtered and the filtrate concentrated. The residue was dissolved in ethyl acetate and washed with 10% sodium hydroxide, water and brine. The organic phase was extracted with dilute hydrochloric acid and the aqueous phase was basified to pH 7.5 and extracted with ethyl acetate. The organic phase was washed with brine, dried with magnesium sulfate, concentrated and treated with hydrogen chloride to give 6-chloro-2,3,4,5-tetrahydro-3-methyl-9-phenoxy-1H-3-benzazepine hydrochloride; mp 215-217°C.

Example 2

6-Chloro-2,3,4,5-tetrahydro-9-[(4-methoxyphenyl)methoxyl-3-methyl-1H-3-benzazepine

A solution of 9-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepin-6-ol (0.84 g, 4 mmol) in dimethylformamide (10 ml) was treated with a 50% dispersion of sodium hydride in mineral oil (0.23 g, 4.9 mmol), stirred for 10 minutes and treated with a solution of 4-methoxybenzyl chloride in dimethylformamide (4 ml). The mixture was heated to 60°C for 2 hours, poured into cooled aqueous sodium hydroxide and extracted with ethyl acetate. The organic phase was dried, concentrated and the residue was chromatographed on silica gel eluted with a methanol-methylene chloride gradient (1:99-3.5:96.5). Fractions containing the product were pooled, concentrated and treated with maleic acid to give 6-

chloro-2,3,4,5-tetrahydro-9-[(4-methoxyphenyl)methoxy]-3-methyl-1H-3-benzazepine maleate; mp 177-179°C.

Examples 3-12

6-Chloro-9-[(2,6-dimethoxyphenyl)methoxyl-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine

6-Chloro-9-[(4-chlorophenyl)methoxyl-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine

6-Chloro-2,3,4,5-tetrahydro-3-methyl-9-(2-phenylethoxy)-1H-3-benzazepine

6-Chloro-2,3,4,5-tetrahydro-9-[2-(2-methoxyphenyl)ethoxyl-3-methyl-1H-3-benzazepine

6-Chloro-2,3,4,5-tetrahydro-9-[2-(3-methoxyphenyl)ethoxyl-3-methyl-1H-3-benzazepine

6-Chloro-2,3,4,5-tetrahydro-9-[2-(3,4-dimethoxyphenyl)ethoxyl-3-methyl-1H-3-benzazepine

6-Chloro-2,3,4,5-tetrahydro-3-methyl-9-[(3-phenyl-2-propenyl)oxyl-1H-3-benzazepine

6-Chloro-2,3,4,5-tetrahydro-3-methyl-9-[2-phenoxyethoxyl-1H-3-benzazepine

6-Chloro-9-[2-(2,6-dimethoxyphenoxy)ethoxyl-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine

6-Chloro-9-[2,3-dihydrobenzodioxin-2-yl)methoxyl-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine

Using the general procedure of Example 2, replacing 4-methoxybenzyl chloride with 2,6-dimethoxybenzyl

chloride, 4-chlorobenzyl chloride, 2-phenylethyl bromide, 2-(2-methoxyphenyl)ethyl 4-methylbenzenesulfonate, 2-(3-methoxyphenyl)ethyl 4-methylbenzenesulfonate, 2-(3,4-dimethoxyphenyl)ethyl chloride, cinnamyl chloride, 2-(phenoxy)ethyl bromide, 2-(2,6-dimethoxyphenyl)ethyl bromide and 2,3-dihydrobenzodioxin-2-methanol methanesulfonate gave:

6-chloro-9-[(2,6-dimethoxyphenyl)methoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine maleate; mp 112.5-113.5°C

6-chloro-9-[(4-chlorophenyl)methoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine maleate; mp 189-190°C.

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-(2-phenylethoxy)-1H-3-benzazepine hydrochloride; mp 185-186.5°C.

6-chloro-2,3,4,5-tetrahydro-9-[2-(2-methoxyphenyl)ethoxy]-3-methyl-1H-3-benzazepine maleate; mp 153.5-155°C.

6-chloro-2,3,4,5-tetrahydro-9-[3-(3-methoxyphenyl)ethoxy]-3-methyl-1H-3-benzazepine maleate; mp 101-104.5°C

6-chloro-2,3,4,5-tetrahydro-9-[2-(3,4-dimethoxyphenyl)ethoxy]-3-methyl-1H-3-benzazepine hydrochloride; mp 70°C

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[(3-phenyl-2-propenyl)oxy]-1H-3-benzazepine hydrochloride; mp 157-5-162.5°C

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-(2-phenoxyethoxy)-1H-3-benzazepine hydrochloride; mp 150-152°C

6-chloro-9-[2-(2,6-dimethoxyphenoxy)ethoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine hydrochloride; mp 157-159°C

6-chloro-9-[2,3-dihydrobenzodioxin-2-yl)methoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine maleate; mp 58-60°C.

Example 13

6-Chloro-2,3,4,5-tetrahydro-3-methyl-9-[4-(4-nitrophenyl)butoxyl-1H-3-benzazepine

A solution of 4-(4-nitrobenzene)butanol (2.17 g, 11 mmol) and benzyl triethylammonium chloride (0.1 g) in methylene chloride (20 ml) was treated with 30% sodium hydroxide, stirred, cooled to -5°C and treated with methanesulfonyl chloride (1.9 g, 16.7 mmol) in methylene chloride (10 ml). The mixture was stirred at -5°C and then at 25°C for 16 hours. The organic phase was washed with water, dried with sodium sulfate and concentrated. The residue was triturated with ethyl ether to give 4-(4-nitrobenzene)butyl methanesulfonate (methanol); mp 48.5-49.5°C.

Using the general procedure of Example 2, replacing 4-methoxybenzyl chloride with 4-(4-nitrobenzene)butanol methanesulfonate gave 6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[4-(4-nitrophenyl)butoxy]-1H-3-benzazepine (methanol); mp 79-80°C

Example 14

9-[4-(4-Aminophenyl)butoxyl-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine

A mixture of 6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[4-(4-nitrophenyl)butoxy]-1H-3-benzazepine (0.28 g, 0.7 mmol) and platinum oxide in ethanol was shaken under hydrogen for 1 hour, filtered and the filtrate was concentrated, dissolved in ethyl ether and treated with ethereal hydrogen chloride to give 9-[4-(4-aminophenyl)butoxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine dihydrochloride hydrate (methanol-ethyl acetate); mp 150°C (dec.).

Example 15

9-[4-(4-Amino-3-iodophenyl)butoxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine

A stirred solution of 9-[4-(4-aminophenyl)butoxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine (227 mg, 0.6 mmol) in acetic acid (5 ml) was treated with sodium iodide (100 mg, 0.6 mmol) in water, treated with 30% hydrogen peroxide (97 mg, 0.85 mmol) and stirred for 2 hours. The mixture was treated with sodium iodide (25 mg, 0.15 mmol) and hydrogen peroxide (25 mg, 0.22 mmol), stirred for 1 hour and treated with sodium metabisulfite (120 mg) in water (1 ml). The mixture was basified with concentrated ammonium hydroxide, extracted with methylene chloride and the organic phase was washed with brine, dried with sodium sulfate and potassium carbonate and concentrated. The residue was chromatographed on silica gel thin layer plates developed with methanol-ethyl acetate-ammonium hydroxide (5:95:1) and the product eluted with the same solvent. The filtrate was concentrated and the residue was dissolved in methanol and treated with ethereal hydrogen chloride to give 9-[4-(4-amino-3-iodophenyl)butoxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine dihydrochloride hydrate (methanol-ethyl ether); mp 151.5-152°C (dec.).

Example 16

6-Chloro-2,3,4,5-tetrahydro-3-methyl-9-[[(3-(4-nitrophenyl)propyl)carbonyl]oxy]-1H-3-benzazepine

A mixture of 9-chloro-2,3,4,5-tetrahydro-1H-3-benzazepin-6-ol (2 g, 9.4 mmol), 4-(4-nitrobenzene)-butanoyl chloride (2.8 g, 12.3 mmol) and triethylamine (1.7 ml, 12.3 mmol) in methylene chloride was stirred,

heated to reflux for 16 hours and concentrated. The residue was dissolved in ethyl ether, washed with 10% sodium hydroxide and water and dried with sodium sulfate to give 6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[((3-(4-nitrophenyl)propyl)-carbonyl)oxy]-1H-3-benzazepine (ethyl ether-hexane); mp 91-93.5°C.

Example 17

9-[((3-(4-Aminophenyl)propyl)carbonyl)oxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine

Using the general procedure of Example 14, replacing 6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[4-(4-nitrophenyl)-butoxy]-1H-3-benzazepine with 6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[((3-(4-nitrophenyl)-propyl)carbonyl)oxy]-1H-3-benzazepine gave 9-[((3-(4-aminophenyl)propyl)carbonyl)oxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine hydrochloride.

Example 18

6-Chloro-2,3,4,5-tetrahydro-3-methyl-9-(3-phenylpropyl)-1H-3-benzazepine

A solution of 9-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepin-6-amine, (10 g, 47.5 mmol) in acetic acid (34 ml) and water (20 ml) was stirred, treated with sulfuric acid (7.5 ml), cooled to 5°C and treated with a solution of sodium nitrite (3.65 g, 53 mmol) in water (7.5 ml) added below the surface over 20 minutes. The mixture was added dropwise under the surface of a stirred mixture prepared from cupric sulfate pentahydrate (14.2 g, 57 mmol) in water (35 ml), potassium cyanide (15.4 g, 240 mmol), ice (24 g), sodium bicarbonate (31.8 g, 380 mmol) in water (36 ml) and toluene (35 ml) at 50-55°C. The mixture was stirred for 15 minutes at 50°C and for 1

hour at 25°C, treated with a solution of sodium bicarbonate (70 g) in water (700 ml) to pH 8 and then with 10% sodium hydroxide (300 ml). The mixture was extracted with ethyl acetate and the organic phase was washed with aqueous sodium hydroxide and brine, dried with magnesium sulfate and concentrated. The residual oil was treated with ethereal hydrogen chloride to give 8.3 g (68%) of 9-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine-6-carbonitrile; mp 288-290°C.

A solution of 9-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine-6-carbonitrile (3.1 g, 14 mmol) in 90% formic acid (40 ml) was treated with Raney® nickel (3.1 g), stirred and heated to reflux for 3 hours. Additional Raney nickel (17 g) and 90% formic acid (85 ml) were added over the next 12 hours and the mixture was stirred for an additional 3 hours. The mixture was cooled, filtered and the filter cake washed with 45% formic acid. The filtrate was concentrated, basified with 10% sodium hydroxide, extracted with ethyl acetate and the organic phase was washed, dried and concentrated to give 3 g of 9-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine-6-carboxaldehyde.

A solution of triethyl phosphonoacetate (1.9 g, 8.6 mmol) in tetrahydrofuran (200 ml) was stirred and treated with a 50% dispersion of sodium hydride in mineral oil (0.45 g, 9.4 mmol), stirred for 15 minutes and treated with a solution of 9-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine-6-carboxaldehyde (2.2 g, 9.0 mmol) in tetrahydrofuran (270 ml). The mixture was stirred for 16 hours, concentrated, dissolved in ethyl ether and washed with water and brine. The organic phase was dried with magnesium sulfate and concentrated to give 2.6 g of ethyl (E)-3-(9-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepin-6-yl)-2-propenoate.

A solution of ethyl (E)-3-(9-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepin-6-yl)-2-propenoate (2.6 g, 8.9 mmol) in ethanol (150 ml) was treated with

concentrated hydrochloric acid (18 drops) and platinum oxide (0.11 g) and shaken under hydrogen (40 psi) for 2 hours, filtered and concentrated. The residue was partitioned between cooled ethyl acetate-ethyl ether (3:1) (300 ml) and 5% sodium bicarbonate. The organic phase was washed with water and brine, dried with magnesium sulfate and concentrated to give 2.5 g (96%) of ethyl 9-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine-6-propanoate.

A suspension of lithium aluminum hydride (0.55 g, 14.6 mmol) in tetrahydrofuran (20 ml) was stirred, heated to reflux and treated with a solution of ethyl 9-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine-6-propanoate (2.1 g, 7 mmol) in tetrahydrofuran (25 ml). The mixture was stirred at reflux for 3 hours, cooled and carefully treated with water (1.65 ml) and 10% sodium hydroxide (0.55 ml). The mixture was stirred at 25°C, filtered and the filtrate was concentrated. The residue was dissolved in ethyl acetate-ethyl ether (4:1) (160 ml) and washed with water, 5% sodium hydroxide and water, filtered, dried with magnesium sulfate and concentrated. The residue was partitioned between ethyl acetate-ethyl ether (2:1) and 3N hydrochloric acid. The aqueous phase was washed with ethyl ether, basified with aqueous sodium hydroxide and extracted with ethyl acetate-ethyl ether (2:1). The organic phase was washed with water and brine, dried with magnesium sulfate and concentrated. The residue was dissolved in ethyl ether and treated with ethereal hydrogen chloride to give 9-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine-6-propanol hydrochloride; mp 218.5-223.5°C.

A solution of 9-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine-6-propanol (0.8 g, 3 mmol) in methylene chloride (30 ml) was stirred at 5°C and treated with thionyl chloride (40 ml). The mixture was stirred for 10 minutes at 5°C, 15 minutes at 25°C, 3 hours at 55°C and 16 hours at 25°C. The mixture was concentrated to give

0.96 g of 6-chloro-9-(3-chloropropyl)-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine hydrochloride.

A mixture of cuprous bromide (0.35 g, 2.5 mmol) in tetrahydrofuran (7 ml) was stirred, cooled to -25°C, treated with 2M phenyllithium in cyclohexane-ethyl ether (7:3) (3 ml, 5.9 mmol) and stirred for 20 minutes. The mixture was treated with 6-chloro-9-(3-chloropropyl)-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine hydrochloride (0.27 g, 0.87 mmol), stirred for 20 minutes at -25°C and 1 hour at 25°C . The mixture was heated to 75°C for 3 hours and then stirred at 25°C for 16 hours. The mixture was treated with water-ammonium hydroxide (2:1) (60 ml) and extracted with ethyl ether. The organic phase was washed with 10% sodium hydroxide, water and brine, dried with magnesium sulfate and concentrated. The residue was chromatographed on alumina-GF preparative thin layer plates developed with ethyl acetate-hexane (1:9). The product was eluted with ethyl acetate, concentrated, dissolved in ethyl ether and treated with ethereal hydrogen chloride to give a gum. The supernatant was decanted and the gum triturated with ethyl ether to give 6-chloro-2,3,4,5-tetrahydro-3-methyl-9-(3-phenylpropyl)-1H-3-benzazepine; mp 118.5-126°C.

## EXAMPLE 19

An oral dosage form for administering the presently invented compounds is produced by screening, mixing, and filling into a hard gelatin capsule ingredients in the proportions shown in Table II, below.

Table II

| Ingredients | Amounts |
|---|---|
| 6-chloro-2,3,4,5-tetrahydro-3-methyl-9-(2-phenylethoxy)-1H-3-benzazepine | 50 mg |
| magnesium stearate | 5 mg |
| lactose | 75 mg |

EXAMPLE 20

The sucrose, calcium sulfate dihydrate and Formula (I) compound shown in Table III below, are mixed and granulated with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, screened and compressed into a tablet.

Table III

| Ingredients | Amounts |
|---|---|
| 6-chloro-2,3,4,5-tetrahydro-3-methyl-9-(2-phenylethoxy)-1H-3-benzazepine | 100 mg |
| calcium sulfate dihydrate | 150 mg |
| sucrose | 20 mg |
| starch | 10 mg |
| talc | 5 mg |
| stearic acid | 3 mg |

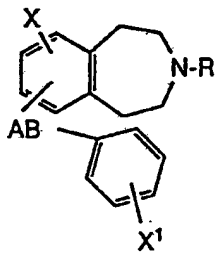
EXAMPLE 21

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-(2-phenylethoxy)-1H-3-benzazepine 75 mg, is dispersed in 25 ml of normal saline to prepare an injectable preparation.

While the preferred embodiments of the invention are illustrated by the above, the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming within the scope of the following claims is reserved.

What is claimed is:

1. A compound having the formula:




in which:

X is H, Cl, Br, F, I, $CF_3$, $C_{1-6}$alkyl, $COR^1$, $CO_2R^2$, $CONR^2R^2$, CN, $NO_2$, $NR^3R^4$, $OR^3$, $SR^1$, $SCF_3$, or any accessible combination thereof up to three substituents;

R is H, $C_{1-6}$alkyl, or $C_{3-5}$alkenyl;

B is absent or present as O or S;

A is $-OCO(CH_2)_{1-4}-$, $-OCH_2CH=CH-$, $-CO_2(CH_2)_{1-4}-$, $-(CH_2)_{0-6}-$, or $-(CH_2)_nZ(CH_2)_m-$, wherein when B is absent, n is 0-4 and m is 0-5, with the proviso that m and n taken together are no greater than 5, and when B is present, n is 0-4 and m is 1-5, with the proviso that m and n taken together are no greater than 5;

Z is O or S;

each $R^1$ independently is $C_{1-6}$alkyl or $(CH_2)_{0-6}$phenyl;

each $R^2$ independently is H, $C_{1-6}$alkyl, or $(CH_2)_{0-6}$phenyl;

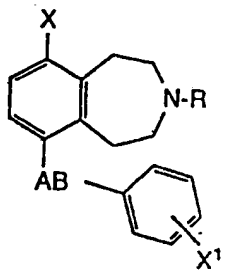
$R^3$ is H, $C_{1-6}$alkyl, CHO, $COR^1$, or $SO_2R^1$;

$R^4$ is H or $C_{1-6}$alkyl; and

$X^1$ is H, Cl, Br, F, I, $CF_3$, $C_{1-6}$alkyl, $COR^1$, $CO_2R^2$, $CONR^2R^2$, CN, $NO_2$, $NR^3R^4$, $OR^3$, $SR^1$, $SCF_3$ or any accessible combination thereof up to five substituents;

or a pharmaceutically acceptable salt thereof, provided that when X is H taken three times, Cl, Br, F, $CF_3$, $CH_3$, $OCH_3$, di-$OCH_3$, OH, di-OH, $NO_2$, $NH_2$, $OC(O)C_{1-6}$alkyl, or di-$CO(O)C_{1-6}$alkyl, B is absent, and A is S, $X^1$ is not H taken five times, Cl, di-Cl, F, OH, $NO_2$, $CH_3$, $CF_3$, or $OCH_3$.

2. A compound of claim 1 having the formula:




in which:

X is H, Cl, Br, F, I, $CF_3$, $C_{1-6}$alkyl, $COR^1$, $CO_2R^2$, $CONR^2R^2$, CN, $NO_2$, $NR^3R^4$, $OR^3$, $SR^1$, or $SCF_3$,

R is H, $C_{1-6}$alkyl, or $C_{3-5}$alkenyl;

B is absent or present as O or S;

A is $-OCO(CH_2)_{1-4}-$, $-OCH_2CH=CH-$, $-CO_2(CH_2)_{1-4}-$, $-(CH_2)_{0-6}-$, or $-(CH_2)_nZ(CH_2)_m-$, wherein when B is absent, n is 0-4 and m is 0-5, with the proviso that m and n taken together are no greater than 5, and when B is present, n is 0-4 and m is 1-5, with the proviso that m and n taken together are no greater than 5;

Z is O or S;

each $R^1$ independently is $C_{1-6}$alkyl or $(CH_2)_{0-6}$phenyl;

each $R^2$ independently is H, $C_{1-6}$alkyl, or $(CH_2)_{0-6}$phenyl;

$R^3$ is H, $C_{1-6}$alkyl, CHO, $COR^1$, or $SO_2R^1$;

$R^4$ is H or $C_{1-6}$alkyl; and

$X^1$ is H, Cl, Br, F, I, $CF_3$, $C_{1-6}$alkyl, $COR^1$, $CO_2R^2$, $CONR^2R^2$, CN, $NO_2$, $NR^3R^4$, $OR^3$, $SR^1$, $SF_3$, or any accessible combination thereof up to five substituents;

or a pharmaceutically acceptable salt thereof, provided that when X is H, Cl, Br, F, $CF_3$, $CH_3$, $OCH_3$, OH, $NO_2$, $NH_2$, or $OC(O)C_{1-6}$alkyl, B is absent, and A is S, $X^1$ is not H taken five times, Cl, di-Cl, F, OH, $NO_2$, $CH_3$, $CF_3$, or $OCH_3$.

3. A compound of claim 2 wherein X is Cl, Br, F, or I.

4. A compound of claim 3 wherein R is $CH_3$.

5. A compound of claim 4 which is 6-chloro-2,3,4,5-tetrahydro-3-methyl-9-(2-phenylethoxy)-1H-3-benzazepine or a pharmaceutically acceptable salt thereof.

6. A compound of claim 4 which is:

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-phenoxy-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-9-[(4-methoxyphenyl)methoxy]-3-methyl-1H-3-benzazepine;

6-chloro-9-[(2,6-dimethoxyphenyl)methoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

6-chloro-9-[(4-chlorophenyl)methoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-9-[2-(2-methoxyphenyl)ethoxy]-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-9-[2-(3-methoxyphenyl)ethoxy]-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-9-[2-(3,4-dimethoxyphenyl)ethoxy]-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[(3-phenyl-2-propenyl)oxy]-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[2-phenoxyethoxy]-1H-3-benzazepine;

6-chloro-9-[2-(2,6-dimethoxyphenoxy)ethoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[4-(4-nitrophenyl)butoxy]-1H-3-benzazepine;

9-[4-(4-aminophenyl)butoxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

9-[4-(4-amino-3-iodophenyl)butoxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[((3-(4-nitrophenyl)propyl)carbonyl)oxy]-1H-3-benzazepine;

9-[((3-(4-aminophenyl)propyl)carbonyl)oxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine; or

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-(3-phenylpropyl)-1H-3-benzazepine; or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising a compound of claim 1 and a suitable pharmaceutical carrier.

8. A pharmaceutical composition of claim 7 wherein the compound is 6-chloro-2,3,4,5-tetrahydro-3-methyl-9-(2-phenylethoxy)-1H-3-benzazepine or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition of claim 7 wherein the compound is:

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-phenoxy-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-9-[(4-methoxyphenyl)methoxy]-3-methyl-1H-3-benzazepine;

6-chloro-9-[(2,6-dimethoxyphenyl)methoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

6-chloro-9-[(4-chlorophenyl)methoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-9-[2-(2-methoxyphenyl)ethoxy]-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-9-[2-(3-methoxyphenyl)ethoxy]-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-9-[2-(3,4-dimethoxyphenyl)ethoxy]-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[(3-phenyl-2-propenyl)oxy]-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[2-phenoxyethoxy]-1H-3-benzazepine;

6-chloro-9-[2-(2,6-dimethoxyphenoxy)ethoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[4-(4-nitrophenyl)butoxy]-1H-3-benzazepine;

9-[4-(4-aminophenyl)butoxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

9-[4-(4-amino-3-iodophenyl)butoxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[((3-(4-nitrophenyl)propyl)carbonyl)oxy]-1H-3-benzazepine;

9-[((3-(4-aminophenyl)propyl)carbonyl)oxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine; or

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-(3-phenylpropyl)-1H-3-benzazepine; or a pharmaceutically acceptable salt thereof.

10. A method of antagonizing α-adrenergic receptors in mammals which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

11. A method of claim 10 wherein the compound is 6-chloro-2,3,4,5-tetrahydro-3-methyl-9-(2-phenylethoxy)-1H-3-benzazepine or a pharmaceutically acceptable salt thereof.

12. A method of claim 10 wherein the compound is:

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-phenoxy-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-9-[(4-methoxyphenyl)methoxy]-3-methyl-1H-3-benzazepine;

6-chloro-9-[(2,6-dimethoxyphenyl)methoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

6-chloro-9-[(4-chlorophenyl)methoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-9-[2-(2-methoxyphenyl)ethoxy]-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-9-[2-(3-methoxyphenyl)ethoxy]-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-9-[2-(3,4-dimethoxyphenyl)ethoxy]-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[(3-phenyl-2-propenyl)oxy]-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[2-phenoxyethoxy]-1H-3-benzazepine;

6-chloro-9-[2-(2,6-dimethoxyphenoxy)ethoxy]-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[4-(4-nitrophenyl)butoxy]-1H-3-benzazepine;

9-[4-(4-aminophenyl)butoxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

9-[4-(4-amino-3-iodophenyl)butoxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine;

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-[((3-(4-nitrophenyl)propyl)carbonyl)oxy]-1H-3-benzazepine;

9-[((3-(4-aminophenyl)propyl)carbonyl)oxy]-6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine; or

6-chloro-2,3,4,5-tetrahydro-3-methyl-9-(3-phenylpropyl)-1H-3-benzazepine; or a pharmaceutically acceptable salt thereof.

13. A method of treating hypertension in mammals which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

14. A method of treating congestive heart failure in mammals which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

15. A method of treating peripheral vascular disease in mammals which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

16. A method of treating benign prostatic hypertrophy in mammals which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/07694

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/55; CO7D 223/16
US CL :540/594; 514/213
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/929

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS online - structure search

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US, A, 3,483,185 (Tokolisc et al.) 9 December 1969, see column 2, lines 24 to 45 | 1-2 |
| Y | EP,A, 7070 (Smithkline Corporation) 23 Jan 1980, see examples 1 to 6 | 1 to 9 |
| A | US, A, 4,683,229 (Demarinis et al.) 28 July 1987, see entire document | 1 to 16 |
| A | US, A 4,469,634 (DeMarinis) 4 September 1984. See entire document | 1 to 16 |
| Y | Kaiser, et al., J. Med. Chem. 1980, 23(9), pp. 975-6. "6-(phenylthio)-substituted 2, 3, 4, 5 -tetrahydro - 1H-3-benzazepines, a novel class of Dopamine Receptor Antagonists and Neuroleptics. See entire document | 1 to 9 |
| Y | Ku, et al., J. Org Chem. 1982, 47,3862-3865 "New Synthesis of Some Arylthio - substituted 2, 3, 4, 5 -tetrahydro 1H-3-benzazepines". See entire document | 1 to 9 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | | | |
|---|---|---|---|
| * | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
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| "P" | document published prior to the international filing date but later than the priority date claimed | | |

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|---|---|
| Date of the actual completion of the international search<br>27 OCTOBER 1992 | Date of mailing of the international search report<br>17 DEC 1992 |
| Name and mailing address of the ISA/<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. NOT APPLICABLE | Authorized officer<br>EDWARD WARD<br>Telephone No. (703) 308-1235 |

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# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9102444 SA 54274

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 31/03/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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